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Abstract: OBJECTIVES To analyze the evidence regarding the efficacy of lateral bone augmentation procedures in terms of defect resolution in cases of horizontal ridge deficiencies after implant placement. MATERIALS AND METHODS Included studies met the following inclusion criteria: randomized controlled trials (RCTs) or controlled clinical trials (CCT's), re-entry procedure to assess defect resolution, minimum of 10 patients (5 per group). Meta-analyses were performed whenever possible, including subgroup analysis based on membranes and grafting materials. RESULTS Twenty-eight publications (20 short-term, 8 follow-up studies) were included. The most often used type of intervention was a xenogeneic particulated grafting material (XE) and a resorbable collagen membrane (CM). The mean defect height at baseline amounted to 5.1 mm (range 2.4 - 7.8) and decreased to a mean of 0.9 mm (range 0.2 - 2.2) at re-entry, and the mean defect resolution was 81.3% (range 56.4% - 97.1%). Defect height reduction was not significantly different using CM +XE as control treatment compared to the combined data of the respective test groups [n=11; weighted mean difference (WMD) = -0.006mm; 95% CI, -0.61, 0.60; p=0.985]. The absence of any lateral bone augmentation was less favorable than the conjunction of a membrane and a bone grafting material (n=1; MD = -1.96mm; 95% CI, -3.48, -0.44; p=0.011). The lack of a grafting material was less favorable than the conjunction of grafting material and membrane (n=1; MD = -2.44mm; 95% CI, -4.53, -0.35; p=0.022) and the addition of a membrane compared to a grafting material alone was more favorable (n=3; WMD = 0.97mm; 95% CI, 0.31, 1.64; p=0.004). CONCLUSIONS Lateral bone augmentation is a successful treatment modality. For optimal defect height reduction, a barrier membrane and a grafting material should be combined. This article is protected by copyright. All rights reserved.

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# Efficacy of lateral bone augmentation performed simultaneously with dental implant placement. A systematic review and meta-analysis.

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**ABSTRACT**

**Objectives:** To analyze the evidence regarding the efficacy of lateral bone augmentation procedures in terms of defect resolution in cases of horizontal ridge deficiencies after implant placement.

**Materials and Methods:** Included studies met the following inclusion criteria: randomized controlled trials (RCTs) or controlled clinical trials (CCT's), re-entry procedure to assess defect resolution, minimum of 10 patients (5 per group). Meta-analyses were performed whenever possible, including subgroup analysis based on membranes and grafting materials.

**Results:** Twenty-eight publications (20 short-term, 8 follow-up studies) were included. The most often used type of intervention was a xenogeneic particulated grafting material (XE) and a resorbable collagen membrane (CM). The mean defect height at baseline amounted to 5.1 mm (range 2.4 - 7.8) and decreased to a mean of 0.9 mm (range 0.2 - 2.2) at re-entry, and the mean defect resolution was 81.3 % (range 56.4% - 97.1%). Defect height reduction was not significantly different using CM +XE as control treatment compared to the combined data of the respective test groups [n=11; weighted mean difference (WMD) = -0.006mm; 95% CI, -0.61, 0.60; p=0.985]. The absence of any lateral bone augmentation was less favorable than the conjunction of a membrane and a bone grafting material (n=1; MD = -1.96mm; 95% CI, -3.48, -0.44; p=0.011). The lack of a grafting material was less favorable than the conjunction of grafting material and membrane (n=1; MD = -2.44mm; 95% CI, -4.53, -0.35; p=0.022) and the addition of a membrane compared to a grafting material alone was more favorable (n=3; WMD = 0.97mm; 95% CI, 0.31, 1.64; p=0.004).

**Conclusions:** Lateral bone augmentation is a successful treatment modality. For optimal defect height reduction, a barrier membrane and a grafting material should be combined.

**CLINICAL RELEVANCE**

**Scientific rationale for the study:** Lateral bone augmentation performed simultaneously with dental implant placement is a well-established treatment modality. The efficacy of the procedure and the influence of various biomaterials on short- and longer-term outcomes are insufficiently documented in a systematic review.

**Principal findings**: The overall mean vertical defect resolution amounted to 81.3 % (range 56.4% - 97.1%). Even though the number of studies included in meta-analysis was limited, the combination of a grafting material and a membrane was more favorable compared to a membrane or a grafting material alone or the absence of treatment. The most often used type of intervention was a xenogeneic particulated grafting material (XE) and a resorbable collagen membrane (CM).

**Practical implications:** Guided bone regeneration is a successful treatment modality to obtain defect resolution at implant dehiscence defects. For optimal defect height reduction, a barrier membrane and a grafting material should be combined. CM + XE is the best documented method for GBR.

## INTRODUCTION

The use of dental implants is a common procedure to restore missing teeth in both, removable and fixed prosthodontics. Expected and reported survival rates of dental implants and the respective reconstructions exceed 90% after 5 years (Jung, R. E. et al., 2012, Pjetursson, B. E. et al., 2012). In the early days, dental implants were predominantly placed where a sufficient amount of bone was present. This concept changed based on the needs of esthetics and resulted in a so-called prosthetically-driven implant placement (Grunder, U. et al., 2005). Due to changes of the ridge profile following tooth extraction, the amount of available bone may decrease significantly and additional bone regenerative procedures may be required. For such procedures, various biomaterials are applied, including autogenous, allogenic, xenogeneic and synthetic bone substitute materials as well as resorbable and non-resorbable membranes. From a clinical point of view, two clinical research questions arise: i) which materials render the best outcomes as determined by a defect resolution and longer-term clinical outcome and, ii) is there a need to perform a bone regenerative procedure to treat exposed implant threads in the presence of a dehiscence or a fenestration defect. Current evidence supports the use of non-resorbable membranes or resorbable membranes. The shortcoming of non-resorbable membranes are higher rates of wound dehiscences (Zitzmann, N. U. et al., 1997), while for resorbable membranes, a lack of space-maintenance is reported (Mir-Mari, J. et al., 2016). On the level of the biomaterials, autogenous bone has been frequently used, but it may increase patient morbidity due to the harvesting procedures (Nkenke, E. and Neukam, F. W., 2014). In order to overcome this disadvantage and to obtain a slower degradation rate, bone substitute materials have been extensively evaluated (Al-Nawas, B. and Schiegnitz, E., 2014). Still, it is difficult for a clinician to choose from the wide variety of biomaterials and membranes available in the market, and to understand their predictability in terms of defect resolution and longer-term outcomes.

Very recently, controlled clinical studies documented that, in the long-run, implant surfaces might not be fully covered with bone, but still present pleasing soft tissue esthetic and stable levels of the margo mucosae (Benic, G. I. et al., 2012). In addition, studies even suggested that an (un)intended exposition of implant threads to the peri-implant mucosa does only minimally affect peri-implant health and marginal bone levels (Jung, R. E. et al., 2017, Schwarz, F. et al., 2012).

Therefore, the aim of the present systematic review was to analyze the evidence regarding the efficacy of lateral bone augmentation procedures in terms of defect resolution in cases of horizontal ridge deficiencies after implant placement.

## MATERIAL AND METHODS

*Development of the protocol*

The study protocol was designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement. Before the start of the systematic review, a protocol was developed and registered (Prospero ID: 93196) aiming to answer the P.I.C.O. question (Needleman, I. G., 2002) that rendered the following P.I.C.O. definitions:

- *Population:* Patients, older than 18 years and in good general health, requiring the placement of one or more dental implants in sites presenting horizontal ridge deficiencies.
- *Interventions:* Any procedure designed to locally augment the bone laterally around an implant to cover exposed threads in dehiscence or fenestration type defects (simultaneous approach). The following procedures were considered: Guided bone regeneration (GBR) using resorbable or non-resorbable membranes alone or with the addition of bone graft substitutes (autografts, xenografts, alloplasts or allografts) or bone graft substitutes alone, or ridge splitting/expansion techniques.
- *Comparison:* any procedure aimed at lateral bone augmentation (simultaneous) or the absence of treatment.
- *Outcomes:* The mean defect height resolution measured with a caliper or a probe at re-entry (in mm and/or %) was considered the primary outcome (Figure 1). A defect resolution of 100 % or 0 mm remaining defect height is considered as a regeneration up to the implant shoulder. Secondary outcomes were implant survival rates (%), marginal bone levels (MBL), occurrence of biological complications, necessity of re-grafting at re-entry, defect width resolution (Figure 1), probing depth (PD), bleeding on probing (BOP), contour changes of the buccal

peri-implant tissues and changes of position of the mucosal margin. In addition, patient-reported outcomes measures (PROMs) were assessed.

- Study design: Randomized controlled clinical trials (RCTs), controlled clinical trials (CCTs) with a minimum sample size of 10 patients (5 per group) and a re-entry procedure.

*Exclusion criteria*

- Studies assessing interventions aimed at staged horizontal and/or vertical bone augmentation (GBR, bone blocks, distraction osteogenesis, orthognatic surgery, inter-positional grafts, maxillary sinus augmentation, etc.).
- Studies assessing lateral bone augmentation in conjunction with immediate implant placement.
- Preclinical studies in animal models.
- Articles published in a different language than Spanish, English or German.

*Search strategy*

Three electronic databases were used as sources in the search for studies satisfying the inclusion criteria: (1) The National Library of Medicine (MEDLINE via Pubmed); (2) Embase; and (3) Cochrane Central Register of Controlled Trials. These databases were searched for studies published until March 2018. The search was limited to human subjects. A search for gray literature was not attempted. Two independent investigators (ISM/SB) performed the study selection, any doubts or disagreements were discussed with a third investigator (DTH). Prior to the beginning of the data extraction, a calibrating session was performed. Two investigators (ISM/SB) screened 100 titles and abstracts and discussed their potential inclusion/exclusion. Data extraction was performed by two investigators (ISM, SB) in duplicate and thereafter discussed to find an agreement.

All reference lists of the selected studies were checked for cross-references. In addition, the following journals were hand-searched from year 2005 to 2018: *Journal of Clinical Periodontology, Journal of Periodontology, Clinical Oral Implants Research, International*

*Journal of Oral & Maxillofacial Implants, European Journal of Oral Implantology, Implant Dentistry, International Journal of Oral and Maxillofacial Surgery, Journal of Dental Implantology, Journal of Oral and Maxillofacial Surgery*, *Clinical Implant Dentistry and Related Research and Journal of Dental Research.*

*Inclusion of articles reporting on the same population*

Articles reporting on the follow-up of a patient population included for analysis of the primary outcome were also included in the final selection. In case of several follow-up reports, only the longest available follow-up was included, unless there were different outcomes of interest reported in the earlier publications.

*Quality assessment*

The quality of the included studies was assessed independently by one of the reviewers (ISM). The study designs were evaluated according to the Cochrane Collaboration recommendations (Higgins, J. P. et al., 2009). Following these criteria, studies were defined as of low, unclear or high risk of bias.

*Data analyses*

The statistical heterogeneity among studies was assessed using the Q test based on chi-square statistics (Cochran, W. G., 1954) as well as the I2 index (Higgins, J. P. et al., 2003) in order to know the percentage of variation in the global estimate that was attributable to heterogeneity (I2=25%: low; I2=50%: moderate; I2=75%: high heterogeneity).

To summarize and compare studies, mean values of primary (defect height resolution) and secondary quantitative outcomes (defect width resolution, MBL, PD, BOP, CBCT levels, recession) were directly pooled and analyzed with weighted mean differences (WMDs) and 95% confidence intervals (CIs). In the case of dichotomous outcome (exposure events), the estimates of the effect were expressed in risk ratios and 95% CIs. Study-specific estimates was pooled with both the fixed and random- effect models

(DerSimonian, R. and Laird, N., 1986), and the random-effect model results was presented. Three groups of meta-analyses were performed, based on the type of control group, either native resorbable collagen membranes combined with a particulate xenograft (CM+XE), non-resorbable expanded polytetrafluorethylene membranes with any bone substitute (ePTFE+BS) or allograft alone (ALO). In the case of studies with more than two arms, each intervention was compared against the control group. In addition, a subgroup analysis was performed in each meta-analysis on the selected outcome variables using the type of test materials as explanatory variable.

The publication bias was evaluated using the Begg's and Egger's tests for small-study effects for the main outcome variable. A sensitivity analysis of the meta-analysis results was also performed. Forest plots were created to illustrate the effects of the meta-analysis and the global estimations. STATA-14® (StataCorp LP, Lakeway Drive, College Station, Texas, USA) intercooled software was used to perform all analyses. Statistical significance was defined as a p value $<0.05$.

## RESULTS

*1. Study characteristics*

The electronic search provided a total of 1,245 titles/abstracts (for details refer to Figure 2). Out of these, 1,179 were excluded (inter-reader agreement = 95.25 %; kappa = 0.54; p<0.001; 95% CI: 0.44; 0.63). The resulting number of obtained full text articles was 66. The hand search provided a further number of 20 publications, resulting in an overall number of 86 full text articles. Out of these, 58 were excluded (inter-reader agreement = 93.02%; kappa = 0.85, p<0.001; 95% CI: 0.77; 0.98). Finally, 28 publications met the inclusion criteria and were included (Table 1).

*1.1. Exclusion of studies*

If clinical trials were potentially eligible for inclusion, but did not provide data on the primary outcome, authors were contacted to provide, if available, additional data. Reasons for excluding studies were: no surgical re-entry/CBCT data reporting defect resolution (n=20), articles in other language (n=1), case series (n=32), other (e.g. insufficient data, inappropriate control group, longer follow-up available) (n=5) (see reference list "excluded studies").

*1.2. Quality assessment of the included studies*

In table 2, the results of the quality assessment are summarized. Sixteen studies of the included studies were designed as randomized controlled clinical trials (RCTs). Four studies had a controlled clinical trial (CCT) design. In addition, follow-up data were provided in 7 RCTs and one CCT. The full checklist (Cochrane Collaboration's tool for assessing the risk of bias) was applied for RCTs and CCTs. Six studies were considered as low and ten as unclear risk of bias. The remaining studies were considered to have a high risk of bias.

*1.3. Included studies*

The 28 publications meeting the inclusion criteria described RCTs (n=16), CCTs (n=4) or follow-up studies with an RCT design (n=7) or a CCT design (n=1). Publication dates ranged between 1995 and 2017 for the 26 single-center and the two multicenter studies. The studies were performed in University settings (n=25), in private practice (n=2) or combined at the University and private practice (n=1).

*2. RCTs and CCTs short-term data*

Three out of 20 studies had a split-mouth design (all RCTs) and 17 studies a parallel group design. In these studies, two or three types of interventions were reported, whereas in one study, late and delayed implant placement treatments were compared. Overall, 820 patients with a mean age of 52 years had been treated with 1,069 dental implants. Females were 62.3 % and smokers 9.0 %. The smoking status, periodontal and systemic health were, however, poorly reported. The drop-out rate ranged between 0 % and 20.6 %, resulting in a total number of 800 patients providing data for the primary outcome. The observation period ranged between 4 and 18 months. Twenty-six implants were lost, resulting in a cumulative implant survival rate of 97.6 %. Implant survival rates were not affected by the type of treatment (membrane, grafting material, absence of treatment) up to a short-term follow-up of 18 months.

*2.1. Interventions, grafting materials and membranes*

The types of interventions at implants with dehiscence defects are displayed in table 1.

The primary outcome (defect height reduction) was assessed by surgical re-entry procedures after a mean follow-up period of 6.3 months (follow-up range 4-12 months). The baseline and re-entry data on defect height as well as the change are summarized in table 3. The mean defect height at baseline amounted to 5.1 mm (range 2.4 - 7.8) and decreased to a mean of 0.9 mm (range 0.2 - 2.2) at re-entry. This resulted in a mean defect resolution of 81.3 % (range 56.4 - 97.1).

*2.2. Primary outcome*

*2.2.1. Effect of type of membrane*

The most often used type of intervention was the combination of a xenogeneic particulated grafting material with or without autogenous bone particles and a resorbable collagen membrane (n=13). Meta-analyses using a native collagen membrane (CM) in conjunction with a xenogeneic particulated grafting material (XE) as control treatment demonstrated a significant heterogeneity between the studies (I2=67.1%; p=0.001) (Figure 3a). Defect height reduction was not significantly different (weighted mean difference (WMD) = -0.006mm; 95% CI, -0.61, 0.60; p=0.985) compared to the combined data of the respective test groups (n=11) (Figure 3a). The WMD compared to non-resorbable expanded polytetrafluorethylene (ePTFE) plus bone substitute materials (BS) (n=2) (-0.43mm; 95% CI, -0.78, -0.08) was significant (p=0.015) in favor of CM. The use of a synthetic PEG membrane resulted in a significantly more favorable defect height reduction (MD = 1.38mm; 95% CI, 0.39, 2.37; p=0.006) (n=1). All other comparisons did not result in significant inter-group differences (Figure 3a).

The second most commonly used materials were xenogeneic particulated grafting materials with or without autogenous bone particles and a membrane (n=6) (Figure 3b). Non-resorbable ePTFE membranes plus BS resulted in significantly more favorable outcomes (WMD = -1.18mm; 95% CI, -2.28, -0.08; p=0.035) compared to the combined data of the respective test groups (n=5); heterogeneity was large though (I2=88.4%; p<0.001). Based on three comparative studies using synthetic membranes (polylactide/polyglycolide) and BS, ePTFE membranes were significantly more effective (WMD = -1.49mm; 95% CI, -1.93, -1.05; p<0.001) (Figure 3b).

No publication bias for re-entry height changes was detected by Begg (p= 0.755) or Egger tests (p=0.547). The sensitivity analyses for this outcome showed that the exclusion of a single study did not substantially alter any estimate.

*2.2.2. Effect of placing a membrane*

The effect of placing a membrane in addition to a grafting material (autogenous bone chips or allografts) was evaluated in three studies (Fu, J. H. et al., 2014, Park, S. H. et al., 2008, Schlegel, A. K. et al., 1998). GBR performed with a membrane was significantly more favorable (n=2; WMD = 0.97mm; 95% CI, 0.31, 1.64; p=0.004) (Figure 3c) compared to the use of a bone substitute alone.

*2.2.3. Effect of type of grafting material*

The effect of a specific grafting material could not be analyzed due to a large heterogeneity of membranes used in the studies.

*2.2.4. Effect of placing a grafting material*

In one study, implant sites were allocated to two treatment modalities (ePTFE membrane with or without demineralized freeze-dried bone allograft) (DFDBA) (Mattout, P. et al., 1995). Defect height reduction was significantly more favorable in case a BS was placed (n=1; MD = -2.44mm; 95% CI, -4.53, -0.35; p=0.022). The mean success rates (defined as 0% remaining defect height) were 68% (membrane alone) and 90% (membrane plus grafting material).

*2.2.5. Absence of treatment*

In the absence of bone regeneration at small bony dehiscence defects (Jung, R. E. et al., 2017), further buccal bone loss occurred in 42% of the cases compared to 20% of cases with GBR. Meta-analyses demonstrated a significantly more favorable defect height reduction for sites with GBR compared to no treatment (n=1; MD = -1.96 mm; 95% CI, -3.48, -0.44) (p=0.011). The change of the mucosal level (increasing recession) at implant sites undergoing GBR amounted to 0.5mm compared to sites left with exposed implant threads (0.7mm) (MD = 0.15 mm; 95% CI, -1.99, 2.29; p=0.891). Implant survival rates and peri-implant health were, however, not affected by the absence of treatment up to 18 months (Jung, R. E. et al., 2017).

*2.3. Secondary outcomes*

*2.3.1. Necessity for re-grafting*

In 5 studies, the *necessity for re-grafting* (upon re-entry) was described. In three studies, no implant site needed an additional bone regenerative procedure (Becker, J. et al., 2009, Naenni, N. et al., 2017, Park, S. H. et al., 2008). In two studies, patients in need of re-grafting were excluded from the analysis (Lee, D. W. et al., 2015, Lee, J. H. et al., 2015).

*2.3.2. Re-entry width*

Based on meta-analyses using CM or ePTFE as control membranes, the only significantly different WMD was calculated between CM + XE and ePTFE + BS (n=3) (WMD = 0.52 mm; 95% CI: 0.27, 0.78; p<0.001) in favor of the non-resorbable membrane.

*2.3.3. Membrane exposure*

Twenty studies explicitly reported membrane exposure between implant placement and re-entry (follow-up range 3-12 months). The overall rate of membrane exposure was 22.7% based on 911 sites. Table 4 displays the rate of exposure depending on the type of membrane. Meta-analyses were performed for 11 studies using CM + XE, 5 studies using ePTFE plus BS and three studies using allograft (ALO) or autograft as control treatment. None of the comparisons was significantly different (p>0.05). However, some membranes (cross-linked (x-link) CM, ePTFE, native CM + rhBMP-2, synthetic membranes) had a greater risk of exposure than native CM + XE. Moreover, there was a tendency of synthetic membranes to increase the risk of exposure compared to ePTFE membranes. Exposure of membranes did have a significant effect on defect height reduction (n=2) in favor of ePTFE + BS compared to sites with a synthetic resorbable membrane + BS (WMD = -1.19 mm; 95% CI: -2.31, -0.08; p=0.036).

*2.3.4. Radiographic outcomes*

CBCT data were reported in two studies (Lee, D. W. et al., 2015, Naenni, N. et al., 2017). The change in horizontal thickness at the implant shoulder was significantly more favorable for non-resorbable ePTFE membranes (0.2±0.4mm) than for resorbable

collagen membranes (0.8±0.8mm) during 6 months of healing (Naenni, N. et al., 2017). At 1mm below the implant shoulder, the meta-analysis revealed less favorable results for CM + XE versus ePTFE + XE (WMD = 0.78 mm; 95% CI, 0.36, 1.20; p<0.001) and versus X-link CM + XE (WMD = 0.40 mm; 95% CI, -0.34, 1.14; p=0.292). At 3mm below the implant shoulder, results were less favorable for CM + XE versus ePTFE + XE (WMD = 0.63 mm; 95% CI, 0.28, 0.98; p<0.001) and versus X-link CM + XE (WMD = 0.70 mm; 95% CI, -0.01, 1.41; p=0.052) (Lee, D. W. et al., 2015, Naenni, N. et al., 2017).

*2.3.5. Biological complications*

The reported biological complications up to 18 months included: implant exposure, barrier exposure, soft tissue dehiscence, peri-implantitis, recurrent bone loss and bone loss >1.5mm. The mean complication rate was 20.8% based on 144 implant sites. This data does not include the above-mentioned, specifically reported rate of membrane exposure.

*2.3.6. Patient-reported outcomes measures (PROMs)*

None of the studies assessed these outcomes.

*3. RCTs and CCTs follow-up*

Out of 8 follow-up studies, 7 had a RCT design and one study a CCT design. All of the studies with RCT design reported on two different types of interventions and 3 were split-mouth studies. Overall, the studies provided data on 142 patients and a total number of 298 dental implants. The drop-out rate ranged between 9.1 % and 64.8 %. Females accounted for 68.4 % of the patients. The observation period ranged between 36 and 150 months. The survival rate of implants after a mean follow-up of 76.5 months was 95.0%. Implant survival rates were not affected by the type of treatment (membrane, grafting material, sites with exposed implant threads) up to 76.5 months of follow-up.

3.1. Interventions, grafting materials and membranes

The original interventions at implants with dehiscence defects are displayed in Table 1.

The most often used type of intervention was the combination of a xenogeneic particulated grafting material and a resorbable collagen membrane (n=5). The second most commonly used materials were xenogeneic particulated grafting materials with or without autogenous bone particles and an ePTFE membrane (n=2).

*3.2. Outcome measures*

*3.2.1. Marginal bone levels*

Combined mesial and distal marginal bone level changes based on 3 studies (Basler, T. et al., 2018, Jung, R. E. et al., 2013, Ramel, C. F. et al., 2012) at a mean follow-up of 74 months (range 36-150) were -0.19mm (range 0.04 to -0.61). Mesial and distal values were reported separately in one study (Jung, R. E. et al., 2009). The changes from baseline (insertion of prosthetic reconstructions) to 5 years were -0.07 mm (mesial, rhBMP-2 group), -0.11 mm (distal, rhBMP-2 group), -0.03 mm (mesial, control without rhBMP-2), to -0.13 mm (distal, control without rhBMP-2).

*3.2.2. Biological complications*

The reported biological complications after a mean follow-up of 56.8 months (36-96) included: recurrent bone loss, mucositis, peri-implantitis, implant exposure, barrier exposure, soft tissue dehiscence, peri-implantitis, recurrent bone loss and bone loss >1.5mm. The mean complication rate was 14.8% based on 223 implant sites. The mean complication rate for non-resorbable ePTFE membranes amounted to 13.9% based on 43 sites and the mean complication rate for resorbable collagen membranes was 13.6% based on 147 sites. The resorbable x-linked and polyethylene glycol membranes had complication rates of 44.4% and 16.6% based on 9 and 18 sites respectively.

*3.2.3. BOP/PD/level of the mucosa*

Final PD values were reported in 4 studies (Basler, T. et al., 2018, Jung, R. E. et al., 2013, Jung, R. E. et al., 2009, Schwarz, F. et al., 2017) and amounted to 3.4mm (2.4 to 3.9). PD changes amounted to 0.2mm (36 months (Basler, T. et al., 2018)). Bleeding on

probing at the last follow-up (36 and 96 months respectively) ranged between 11.0 and 48.1% (Basler, T. et al., 2018, Schwarz, F. et al., 2017). The level of the mucosa shifted more apically ranging between 0.1 and 0.6mm (Jung, R. E. et al., 2013).

*3.2.4. Contour changes*

Contour changes at the buccal aspect of the implant sites between crown insertion and the 3-year follow-up were evaluated by means of superimposition of the surface STL files and measurement of the mean distance between the surfaces in the relevant area. The changes amounted to -0.3mm without significant differences between non-resorbable and resorbable membrane sites (Basler, T. et al., 2018).

*3.2.5. Follow-up of implant sites with and without dehiscence defects at re-entry*

One particular study re-grouped the patients at the day of re-entry into three patient groups: i) with complete bone fill (no dehiscence), ii) <1mm dehiscence defect and, iii) >1mm dehiscence defect. The patients were re-examined at 4 years. A higher rate of peri-implantitis and more recession was observed for sites with a larger dehiscence defect (Schwarz, F. et al., 2012).

## DISCUSSION

The present systematic review identified 28 eligible prospective clinical trials (20 studies with shorter-term data; 8 follow-up studies) applying various treatment modalities, grafting materials and membranes for lateral ridge augmentation indications.

The most commonly used treatment option in all included studies was a native collagen membrane (CM) in conjunction with a xenogeneic, particulated grafting material (XE). Meta-analyses applying CM + XE as control group revealed no significantly different WMD compared to the combined data of the respective test groups (n=11). Significant differences, however, were observed in direct comparison to the second most common membrane, a non-resorbable ePTFE membrane in favor of CM for the primary outcome, vertical defect resolution. These data are based on two included studies (Carpio, L. et al., 2000, Naenni, N. et al., 2017) and are to some extent surprising since the use of an ePTFE membrane was considered to be the gold standard for GBR procedure at implant sites with dehiscence defects (Benic, G. I. and Hammerle, C. H., 2014). One has to bear in mind, however, that ePTFE membranes were superior compared to all other comparative treatment modalities if taken as a control group based on meta-analyses in the present systematic review. The comparative therapeutic options encompassed: synthetic membranes (n=3), no grafting material (n=1) and a cross-linked CM (n=1)(Mattout, P. et al., 1995, Schneider, D. et al., 2014, Lorenzoni, M. et al., 1998, Moses, O. et al., 2005). Moreover, the effect of GBR is not only assessed by the defect resolution, but also by the obtained changes in defect width, height as well as the horizontal thickness on the buccal side of the implant. In case, the changes in thickness (buccal side of the implant in a horizontal direction) between post-augmentation and 6 months (at re-entry) are considered, ePTFE membranes are reported to result in significantly more favorable outcomes than CM + XE (Naenni, N. et al., 2017). Still, from a clinical point of view, defect resolution (vertical bone fill) and not the obtained

horizontal thickness at the level of the implant shoulder appear to be more important, bearing in mind that the main goal of GBR procedures is to have exposed implant threads covered by bone. Based on the meta-analyses, it is difficult to recommend a specific treatment modality, since the heterogeneity between the studies was large, applying a plethora of barrier membranes and grafting materials. Moreover, WMDs between the treatment modalities were for the majority of the comparisons <1mm. The clinical impact of such a difference remains questionable.

Guided bone regeneration relies on the principle of applying a membrane that serves as a barrier to prevent soft tissue ingrowth into the defect area (Dahlin, C. et al., 1989). In case of applying a non-form-stable resorbable membrane, the placement of a grafting material has been recommended to prevent a collapse of the augmented site (Strietzel, F. P. et al., 2006, Won, J. Y. et al., 2016). Controversy exists on the need of placing a membrane and on the need of a biomaterial to successfully augment bone at buccal dehiscence defects. The present systematic review clearly revealed more favorable outcomes comparing augmentation procedures with and without membranes. The addition of a barrier membrane resulted in a larger defect height reduction of 0.85 up to 1.51 mm (Fu, J. H. et al., 2014, Park, S. H. et al., 2008, Schlegel, A. K. et al., 1998). These outcomes to some extent contradict preclinical and clinical data suggesting the periosteum alone can serve as a barrier membrane and may be sufficient for bone regenerative procedures for various indications (Yu, Z. et al., 2015).

Originally, barrier membranes were placed without grafting material, thereby maintaining the volume for the blood clot to transform into bone (Schmid, J. et al., 1997), (Buser, D. et al., 1998). Meta-analysis demonstrated significantly more favorable outcomes if a grafting material was placed. The data are based on a clinical study using DFDBA as grafting material in direct comparison to the treatment with membranes (ePTFE) alone (Mattout, P. et al., 1995). The calculated WMD was -2.4 mm.

Biological complications were reported to various extents in the included studies and encompassed implant exposure, barrier exposure, soft tissue dehiscence and marginal

bone loss, in the short-term. Membrane exposure has often been attributed to the use of more form-stable (e.g. cross-linked membrane) or non-resorbable membranes. Even though, the incidence of such complications appears to be high for such membranes, all types of membranes and combinations with grafting materials were affected with the majority of the studies reporting complications rates between 17.5 % and 42.1 %. The clinical impact of such complications might depend on the time-point they occur. Resorbable collagen membranes tend to expose at an early stage (suture removal), synthetic membranes slightly later and non-resorbable membranes appear to be affected even during the later healing phase. Early exposure could in part be related to general wound healing complications associated with flap design and management, swelling following the surgical intervention as well as patient compliance. Delayed membrane exposure might be predominantly attributed to a lack of soft tissue integration due to a relatively smooth surface or to degradation products of synthetic membranes. In contrast, the exposure of cross-linked collagen resorbable membranes has been attributed to the chemical and/or physical properties of the respective barriers that affect its behavior in case of exposure. The clinical impact (e.g. defect height resolution) of such complications has been described in five included studies (Becker, J. et al., 2009, Lorenzoni, M. et al., 1998, Park, S. H. et al., 2008, Nemcovsky, C. E. and Artzi, Z., 2002, Fu, J. H. et al., 2014). Most of the outcomes demonstrated a defect height reduction between 40 % and 60%. No membrane, however, appears to be more favorable and to decrease the number of biological complications at least when looking at the raw data and the incidences. It has been documented in two cross-sectional studies that implant dehiscence defects can be observed on CBCT images at 7 and 10 years post placement of dental implants, thereby indicating a failure of the bone augmentation procedure (Benic, G. I. et al., 2012, Kuchler, U. et al., 2016). Interestingly, these complications did not affect the clinical outcomes at the soft tissue level to the same extent as on the level of the bone, with levels of the marginal mucosae being minimally affected. In a RCT (Jung, R. E. et al., 2017), the need for GBR procedures at small buccal bone dehiscence defects

was evaluated comparing sites with and without GBR. Data up to 18 months, demonstrated that in the absence of bone regeneration, further buccal bone loss occurred in 42% of the cases compared to 20% of cases with GBR and a significantly more favorable defect height reduction for sites with GBR compared to no treatment. On the level of the soft tissues, however, the mucosal level was more favorable for sites without GBR compared to sites undergoing GBR. Implant survival rates and peri-implant health were, however, not affected by the absence of treatment (Jung, R. E. et al., 2017). One might speculate that on the longer-term, exposed implant threads, covered by the peri-implant soft tissues, increase the risk of developing peri-implant diseases. In a 4-year follow-up study of a RCT (Schwarz, F. et al., 2012), implant sites with successful and failed GBR procedures were compared. More mucosal recession, a higher BOP value and therefore a higher risk of developing a peri-implant disease was reported for sites with a minimal (1mm) or advanced (>1mm) residual defect height at re-entry. The latter two prospective clinical studies indicate the need to regenerate buccal peri-implant dehiscence defects to maintain peri-implant health over time.

To some extent disappointing, data on longer-term outcomes following GBR procedures were limited. The data are even more limited since all 8 studies were published by two University groups only (University of Düsseldorf, University of Zurich). Based on available data, radiographic marginal bone level changes appear to be minimal and well in line with data on implants being placed in native bone (Benic, G. I. et al., 2017). Clinical outcome measures such as PD, PI and the stability of the mucosal margin were stable. Moreover, the data (derived from two studies; (Naenni, N. et al., 2017, Lee, J. H. et al., 2015)) on contour changes at the buccal aspect of implant sites having been treated with GBR demonstrated minimal changes over time. On the longer-term, biological complications encompassed recurrent bone loss, peri-implant mucositis and peri-implantitis. The overall complication rate was roughly 15% after a mean follow-up of 5 years. Differences between the membranes were hardly observed, except for an

experimentally x-linked collagen membrane that was reported to have a complication rate of 44% (Schwarz, F. et al., 2017, Becker, J. et al., 2009).

The outcomes of the present systematic review are to some extent limited by the large heterogeneity in terms of applied membranes, grafting materials and the respective combinations. Furthermore, it was rarely reported whether implants were placed rather surgically or prosthetically driven and implant site locations varied across the studies with the majority of the studies not reporting details on this. This might have resulted in including studies with variable implant site locations and potentially different types of defects. In conjunction with a similarly high variability of outcome measures, the data did not allow to draw conclusions being able to identify a superior treatment modality. Moreover, longer-term data were only published by two research groups and based on 5 patient cohorts. Future patient populations following GBR are strongly encouraged to be followed for a longer time-span than just the re-entry procedures. In addition, outcome measures such as PROMs and reporting of early (wound dehiscences versus membrane exposure) and late (peri-implant diseases) biological complications should be reported and harmonized and follow guidelines of recent consensus conferences.

## CONCLUSIONS

Lateral bone augmentation via GBR at sites presenting peri-implant dehiscence defects upon implant placement is a successful treatment modality to obtain defect resolution.

The review predominantly revealed:

- a native collagen membrane (CM) in conjunction with a xenogeneic, particulated grafting material (XE) was the most commonly used treatment option;
- meta-analyses applying CM + XE as control group did not result in a significantly more favorable defect resolution compared to the combined data of the respective test groups (n=11);
- a significantly more favorable defect resolution for CM + XE compared to the second most common membrane, a non-resorbable ePTFE membrane;
- for optimal defect height resolution, a barrier membrane and a grafting material should be combined;
- a rate of biological complications of 20.8%;
- relatively small changes of the buccal contour over 3 years post insertion of final reconstructions and a survival rate of implants after a mean follow-up of 76.5 months of 95.0%.

## CONFLICT OF INTEREST, SOURCE OF FUNDING AND ACKNOWLEDGMENTS

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**FIGURE LEGENDS**

**Figure 1.** The reduction of the defect height at re-entry compared with the measurement prior to augmentation was the primary outcome. Resolution of the defect width was a secondary outcome.

**Figure 2.** Flowchart containing the search strategy and respective selection process.

**Figure 3a.** Forest plot illustrating the results in terms of defect height reduction from meta-analysis of all trials with a resorbable collagen membrane in combination with a particulate xenograft (CM+XE) as a control. ePTFE = expanded polytetrafluorethylene; BS = bone substitute; BMP-2 = recombinant human bone morphogenetic protein 2; beta TCP = beta tri-calcium phosphate.

**Figure 3b.** Forest plot illustrating the results in terms of defect height reduction from the meta-analysis of all trials with a non-resorbable expanded polytetrafluorethylene membrane in combination with any bone substitute (ePTFE+BS) as a control. CM = collagen membrane.

**Figure 3c.** Forest plot illustrating the results in terms of defect height reduction from the meta-analysis of all trials with allograft and no membrane (ALO) as a control. CM = collagen membrane.

**Table 1**. Methodological characteristics of the selected studies, the types of interventions and the outcomes measured. RCT = Randomized clinical trial; CCT = Controlled clinical trial; Follow-up = months(mean); NR = Not reported; ePTFE = expanded polytetrafluorethylene; rhBMP-2 = recombinant human bone morphogenetic protein 2; DFDBA = Demineralized freeze dried bone allograft; beta TCP = beta tri-calcium

phosphate; HA = Hydroxyapatite; IS = Implant survival; SR = success rate (procedure); RN = Regrafting necessity; WR = Width reduction; HR = Height reduction; EX = Membrane exposure / wound dehiscence; EXW = Exposed site width reduction; EXH = Exposed site height reduction; NEXW = Non-exposed site width reduction; NEXH = Non-exposed site height reduction; MBL = Marginal bone levels assessed radiographically (mesial and distal combined); HT0 = horizontal thickness at implant shoulder (CBCT assessment); HT1 = horizontal thickness at 1 mm below the implant shoulder (CBCT assessment); HT3 = horizontal thickness at 3 mm below implant shoulder (CBCT assessment); BC = biological complications (i.e. mucositis, peri-implantitis, bone loss); PPD = Peri-implant probing depth; BOP = Bleeding on probing; ML = Midfacial mucosal level; STV = Soft tissue volume.

**Table 2**. Results of the quality assessment. Cochrane Collaboration's tool for assessing the risk of bias was applied for all studies.

**Table 3**. Results of all studies with a re-entry measurement in terms of defect height. The means and standard deviations (SD) of baseline and re-entry outcomes are displayed as well as the changes. NR = Not reported; ePTFE = expanded polytetrafluorethylene; rhBMP-2 = recombinant human bone morphogenetic protein 2; DFDBA = Demineralized freeze dried bone allograft; beta TCP = beta tri-calcium phosphate; HA = Hydroxyapatite.

**Table 4**. Membrane exposures classified by the type of membrane and the number of sites treated.

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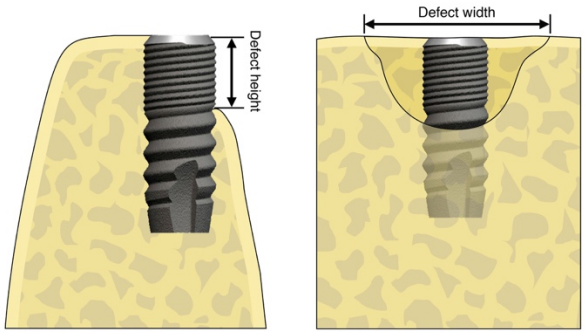


Figure 1

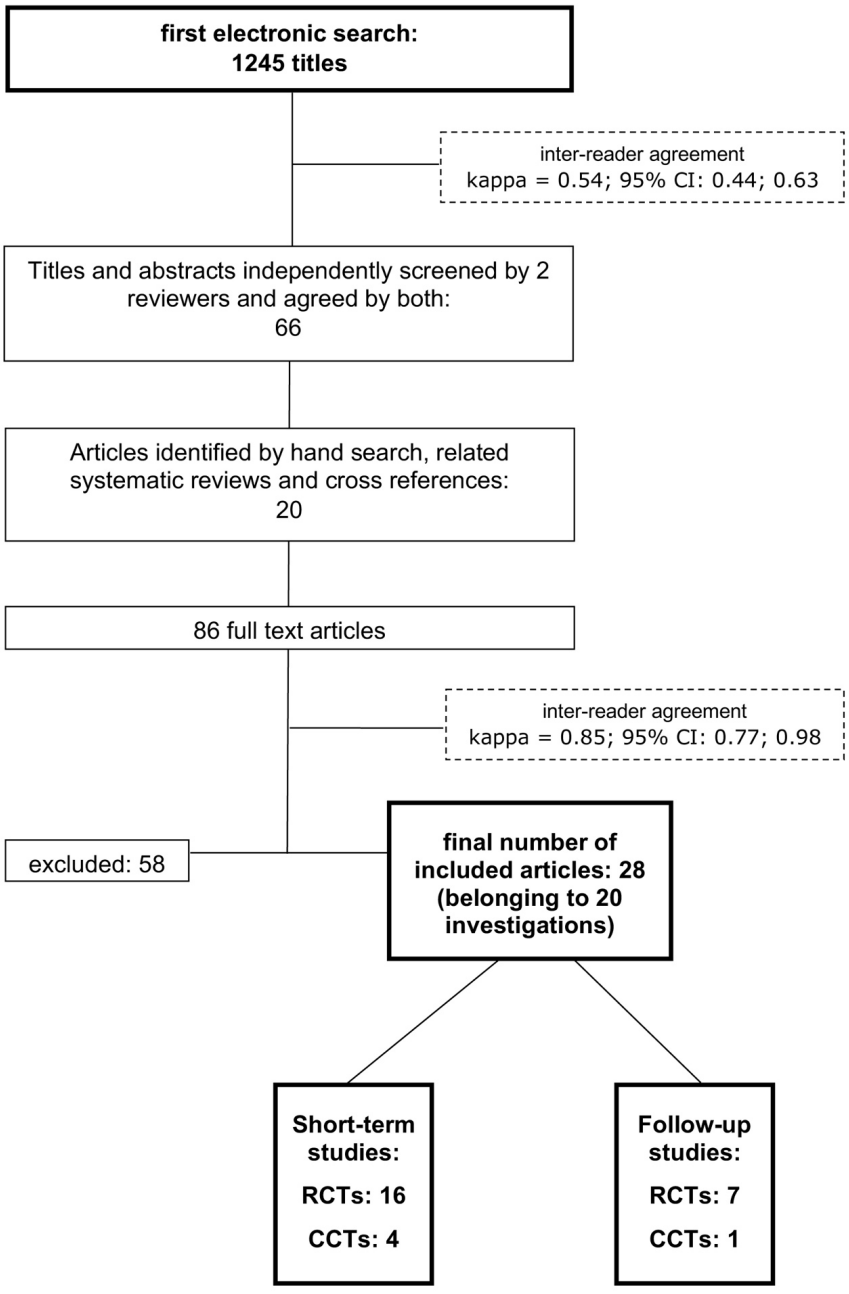


Figure 2

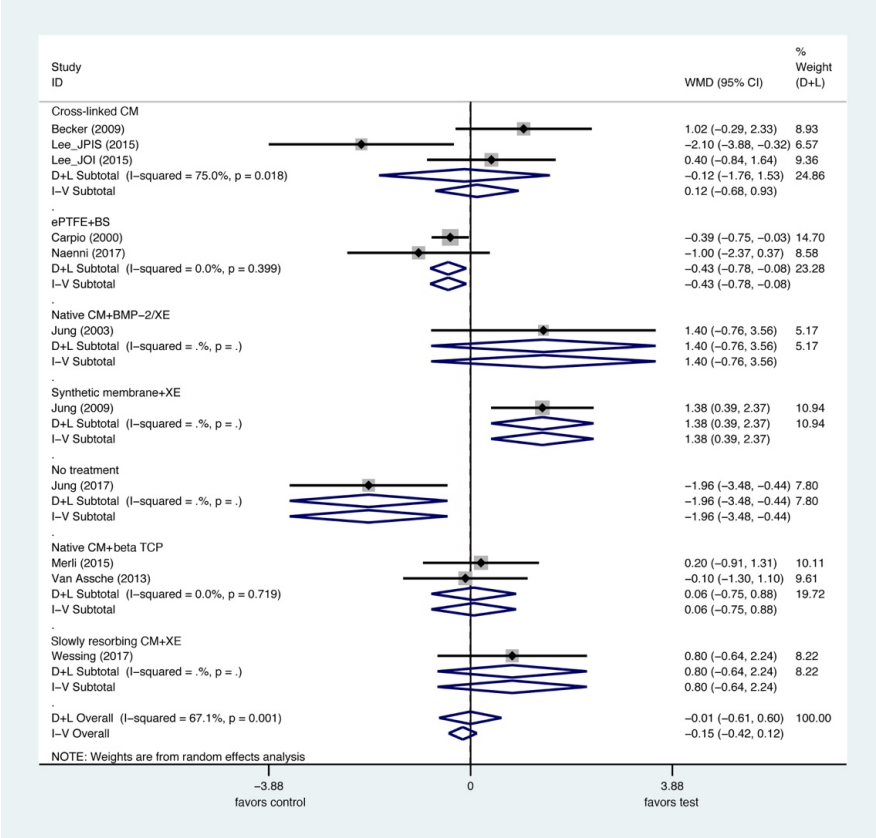


Figure 3a

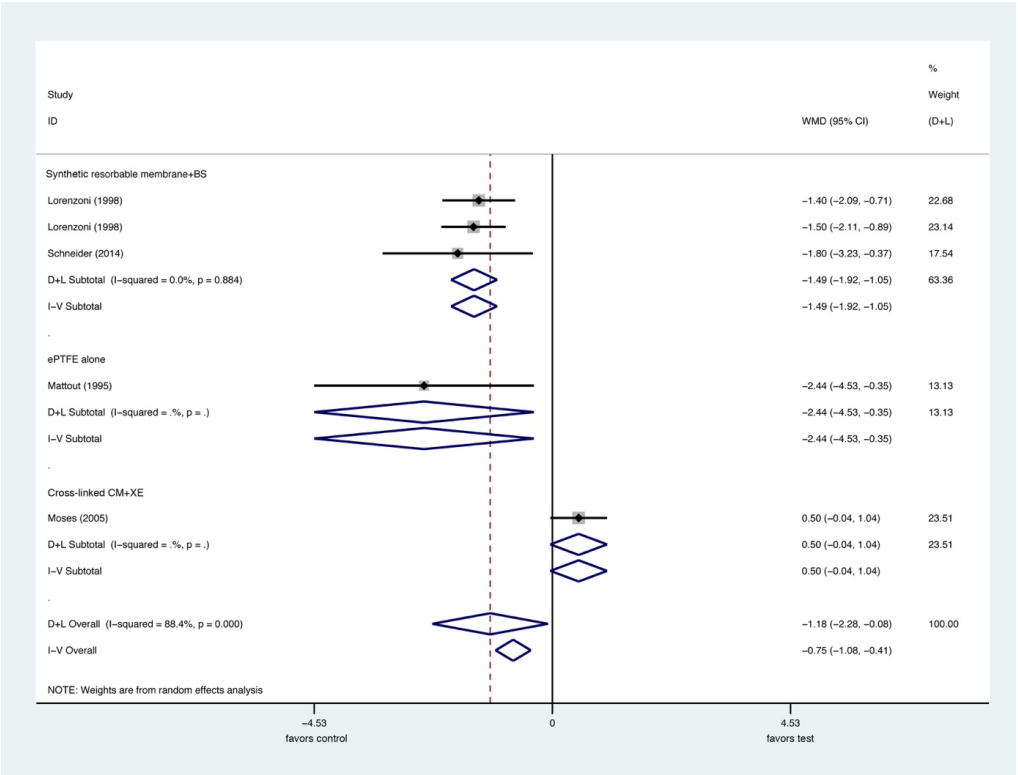


Figure 3b

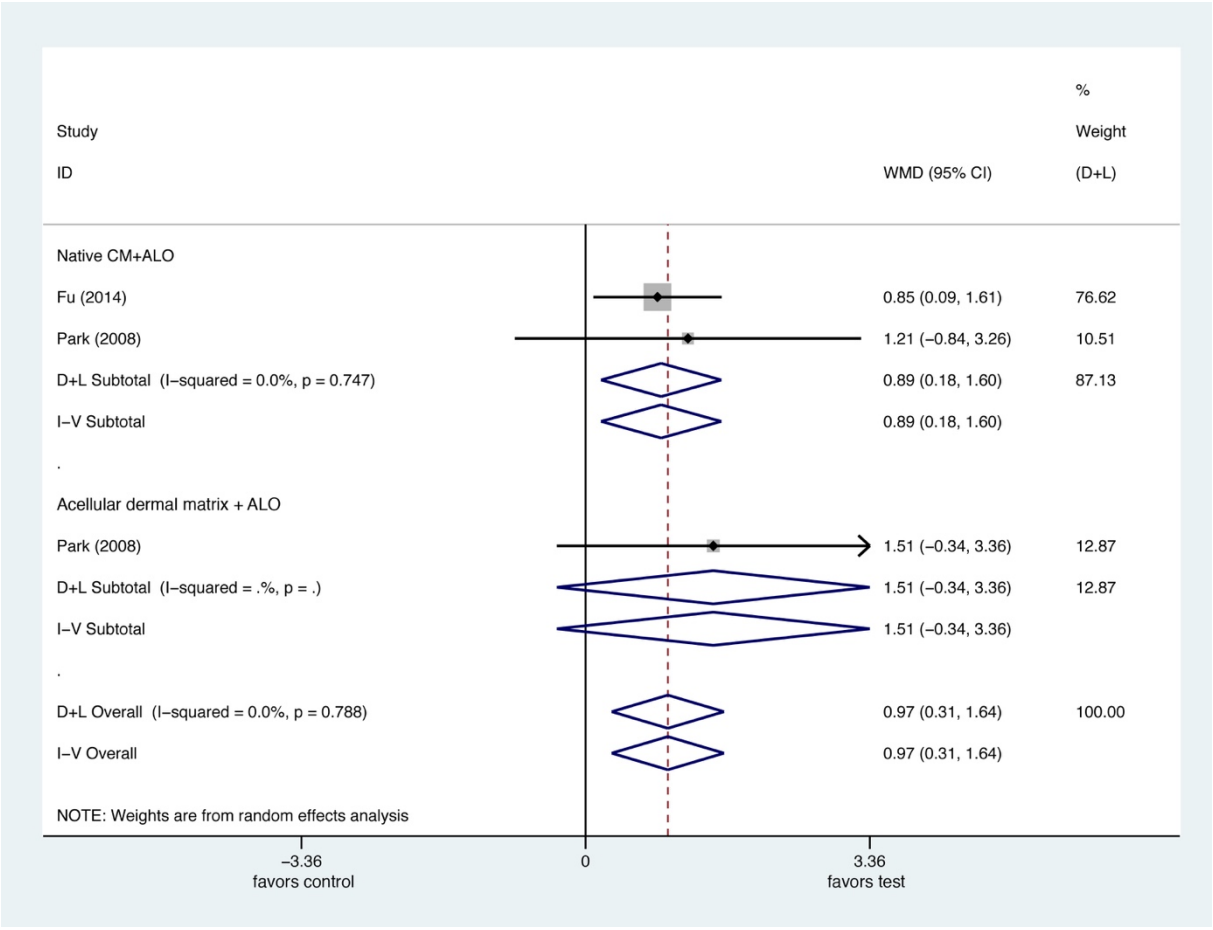
Study
ID
WMD (95% CI)
%
Weight
(D+L)
Native CM+ALO
Fu (2014)
0.85 (0.09, 1.61)
76.62
Park (2008)
1.21 (−0.84, 3.26)
10.51
D+L Subtotal (I−squared = 0.0%, p = 0.747)
0.89 (0.18, 1.60)
87.13
I−V Subtotal
0.89 (0.18, 1.60)
.
Acellular dermal matrix + ALO
Park (2008)
1.51 (−0.34, 3.36)
12.87
D+L Subtotal (I−squared = .%, p = .)
1.51 (−0.34, 3.36)
12.87
I−V Subtotal
1.51 (−0.34, 3.36)
.
D+L Overall (I−squared = 0.0%, p = 0.788)
0.97 (0.31, 1.64)
100.00
I−V Overall
0.97 (0.31, 1.64)
NOTE: Weights are from random effects analysis
−3.36
favors control
0
3.36
favors test

Figure 3c

| Reference | Publication date | Study design | Follow-up (months) | Test patients Base-line (Final) | Control patients Base-line (Final) | Test implants/ Control implants | Interventions Test | Interventions Control | Study outcomes measured |
|---|---|---|---|---|---|---|---|---|---|
| *Interventional studies* | | | | | | | | | |
| Mattout | 1995 | CCT | 6.8 | NR | NR | 11/19 | Non-resorbable ePTFE membrane | DFDBA + non-resorbable ePTFE membrane | IS, SR, WR, HR, EX |
| Zitzmann | 1997 | RCT (split) | 10.7 | 25(25) | 25(25) | 43/41 | Particulate xenograft + non-resorbable ePTFE membrane | Particulate xenograft + resorbable collagen membrane | IS, WR, EX, EXW, NEXW |
| Lorenzoni[a] | 1998 | CCT | 6 | 38(38) | 46(46) | 38/46 | Particulate autologous bone + Polyglycolid, self-reinforced-PGA resorbable membrane | Particulate xenograft and/or particulate autologous bone + non-resorbable ePTFE membrane | IS, HR, EX, EXH, NEXH |
| Lorenzoni[a] | 1998 | CCT | 6 | 38(38) | 45(45) | 38/45 | Particulate autologous bone + Polyglycolid, self-reinforced-PGA resorbable membrane | Particulate xenograft and/or particulate autologous bone + non-resorbable titanium reinforced ePTFE membrane | IS, HR, EX, EXH, NEXH |
| Schlegel | 1998 | RCT (parallel) | 6 | 7(7) | 7(7) | 14/15 | Autogenous bone chips + resorbable polydioxanone membrane | Autogenous bone chips | IS, SR, EX, EXW |
| Carpio | 2000 | RCT (parallel) | 6 | 23(23) | 25(25) | 23/25 | Particulate xenograft + non-resorbable ePTFE membrane | Particulate xenograft + autologous bone + resorbable collagen membrane | IS, SR, WR, HR, EX, BC |
| Nemcovsky | 2002 | CCT | NR | 25(25) | 22(21) | 39/40 | Late implants: Particulate xenograft + resorbable collagen membrane | Delayed implants: Particulate xenograft + resorbable collagen membrane | IS, SR, WR, HR, EX, EXW, EXH, NEXW, NEXH |
| Jung | 2003 | RCT (split) | 6 | 11(10) | 11(10) | 18/16 | Particulate xenograft + resorbable collagen membrane + rhBMP-2 | Particulate xenograft + resorbable collagen membrane | IS, SR, WR, HR, EX |
| Moses[a] | 2005 | CCT | NR | 41(41) | 17(17) | 73/34 | Particulate xenograft or beta TCP + autologous bone + resorbable collagen membrane (Ossix®) | Particulate xenograft or beta TCP + autologous bone + non-resorbable ePTFE membrane | IS, WR, HR, EX |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Moses[a] | 2005 | CCT | NR | 28(28) | 17(17) | 53/34 | Particulate xenograft or beta TCP + autologous bone + resorbable collagen membrane (Bio-Gide®) | Particulate xenograft or beta TCP + autologous bone + non-resorbable ePTFE membrane | IS, WR, HR, EX |
| Park[a] | 2008 | RCT (parallel) | 6 | 9(9) | 9(8) | 9/8 | Cancellous allograft + resorbable collagen membrane | Cancellous allograft | IS, SR, RN, WR, HR, EX, EXH, NEXW, NEXH |
| Park[a] | 2008 | RCT (parallel) | 6 | 9(9) | 9(8) | 9/8 | Cancellous allograft + acellular dermal matrix | Cancellous allograft | IS, SR, RN, WR, HR, EX, EXH, NEXH |
| Becker | 2009 | RCT (parallel) | 4 | 27(23) | 27(26) | 41/37 | Particulate xenograft + resorbable cross-linked collagen membrane | Particulate xenograft + resorbable collagen membrane | IS, SR, RN, WR, HR, EX, EXW, EXH, NEXW, NEXH, BC, PPD, BOP, ML |
| Jung | 2009 | RCT (parallel) | 6 | 19(19) | 18(18) | 19/18 | Particulate xenograft + polyethylenglycol (PEG) resorbable membrane | Particulate xenograft + resorbable collagen membrane | IS, WR, HR, EX |
| Van Assche | 2013 | RCT (split) | 12 | 14(14) | 14(14) | 14/14 | Particulate autologous bone + HA-60% TCP-40% + resorbable collagen membrane | Particulate autologous bone + xenograft + resorbable collagen membrane | IS, WR, HR, NEXH, MBL, BC, PPD, BOP |
| Fu | 2014 | RCT (parallel) | 6 | 13(13) | 13(13) | 13/13 | Allograft + resorbable bovine pericardium membrane | Allograft | IS, WR, HR, EX, EXW, EXH, NEXW, NEXH |
| Schneider | 2014 | RCT (parallel multicenter) | 6 | 19(19) | 21(21) | 19/21 | Particulate xenograft + resorbable polylactide/polyglycolide membrane | Particulate xenograft + titanium reinforced ePTFE membrane | IS, SR, WR, HR, EX, BC |
| Lee[a] | 2015 | RCT (parallel) | 15 | 15(14) | 15(14) | 14/14 | Particulate xenograft + resorbable cross-linked collagen membrane | Particulate xenograft + resorbable collagen membrane | IS, RN, WR, HR, EX, HT1; HT3 |
| Lee[a] | 2015 | RCT (parallel) | 6 | 16(14) | 18(13) | 24/25 | Particulate autogenous or allogenic particles covered by xenograft and resorbable cross-linked collagen membrane | Particulate autogenous or allogenic particles covered by xenograft and resorbable collagen membrane | IS, SR, RN, WR, HR, EX |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Merli | 2015 | RCT (parallel) | 6 | 25(25) | 25(25) | 29/32 | Beta TCP + resorbable porcine pericardium collagen membrane | Particulate xenograft + resorbable collagen membrane | IS, WR, HR, EX, MBL |
| Jung | 2017 | RCT (parallel) | 18 | 12(12) | 10(10) | 15/13 | Implant dehiscences left for spontaneous healing | Particulate xenograft + resorbable collagen membrane | IS, HR, EX, MBL, BC, PPD, BOP, ML |
| Naenni | 2017 | RCT (parallel) | 6 | 13(13) | 14(14) | 13/14 | Particulate xenograft + non-resorbable titanium reinforced ePTFE membrane | Particulate xenograft + resorbable collagen membrane | IS, SR, RN, WR, HR, EX, HT0, HT1, HT3 |
| Wessing | 2017 | RCT (parallel multicenter) | 6 | 24(23) | 25(24) | 24/25 | Particulate xenograft + resorbable collagen membrane (creos xenoprotect®) | Particulate xenograft + resorbable collagen membrane (Bio-Gide®) | IS, SR, WR, HR, EX |
| *Follow-up studies* | | | | | | | | | |
| Zitzmann[a] | 2001 | RCT (split) | 59.1 | 75(66) | 25(22) | 112/41 | Particulate xenograft + non-resorbable ePTFE membrane | Particulate xenograft + resorbable collagen membrane | IS, MBL, BC |
| Jung[b] | 2013 | RCT (split) | 150 | 75(58) | 25(22) | 112/41 | Particulate xenograft + non-resorbable ePTFE membrane | Particulate xenograft + resorbable collagen membrane | IS, MBL, PPD, ML |
| Jung | 2009 | RCT (split) | 60 | 11(10) | 11(10) | 18/16 | Particulate xenograft + resorbable collagen membrane + rhBMP-2 | Particulate xenograft + resorbable collagen membrane | IS, PPD |
| Ramel[a] | 2012 | RCT (parallel) | 36 | 19(18) | 18(18) | 19/18 | Particulate xenograft + polyethylenglycol (PEG) resorbable membrane | Particulate xenograft + resorbable collagen membrane | IS, MBL, BC |
| Jung[b] | 2015 | RCT (parallel) | 60 | 19(15) | 18(17) | 15/17 | Particulate xenograft + polyethylenglycol (PEG) resorbable membrane | Particulate xenograft + resorbable collagen membrane | IS, HR |
| Schwarz[a] | 2012 | CCT (parallel) | 48 | 8(8) | 8(8) | NR | no dehiscence defect | dehiscence defect up to 1mm | BC, PPD, BOP, ML |
| Schwarz[a] | 2012 | CCT (parallel) | 48 | 8(8) | 8(8) | NR | no dehiscence defect | dehiscence defect > 1mm | BC, PPD, BOP, ML |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Schwarz[b] | 2017 | RCT (parallel) | 96 | 20(9) | 22(10) | NR | Particulate xenograft + resorbable cross-linked collagen membrane | Particulate xenograft + resorbable collagen membrane | BC, PPD, BOP, ML |
| Basler | 2018 | RCT (parallel) | 36 | 13(12) | 14(11) | 11/12 | Particulate xenograft + non-resorbable titanium reinforced ePTFE membrane | Particulate xenograft + resorbable collagen membrane | IS, MBL, BC, PPD, BOP, STV |

**Table 1**

| References | SELECTION BIAS | SELECTION BIAS | PERFORMANCE BIAS | DETECTION BIAS | ATTRITION BIAS | SELECTIVE REPORTING BIAS | OTHER POTENTIAL RISK OF BIAS |
|---|---|---|---|---|---|---|---|
| | Sequence Generation | Allocation Concealment | | | | | |
| Becker 2009 | Low | Low | Low | Low | Low | Low | Low |
| Schwarz 2012 | High | High | Low | Low | Low | High | Unclear |
| Schwarz 2017 | High | Low | Low | Low | Low | High | Low |
| Carpio 2000 | Unclear | Unclear | High | Low | Low | Low | Low |
| Fu 2014 | Low | Low | Low | Unclear | Low | Low | Low |
| Jung 2003 | Unclear | Low | Low | Low | Low | Low | Low |
| Jung 2009a | Low | Low | Low | Unclear | Low | Low | Low |
| Jung 2009b | Unclear | Low | Low | Low | Low | Low | Low |
| Ramel 2012 | Unclear | Low | Low | Low | Low | Low | Low |
| Jung 2015 | Unclear | Low | Low | Low | High | High | Low |
| Jung 2017 | Unclear | Low | Low | Unclear | Low | Low | Low |
| Lee DW 2015 | High | High | High | Low | Low | Low | High |
| Lee JH 2015 | Low | Low | Low | Low | Low | Low | Low |
| Lorenzoni 1998 | High | High | High | Unclear | Low | Unclear | Low |
| Mattout 1995 | High | High | High | Low | Low | Low | High |
| Merli 2015 | Low | Low | Low | Low | Low | Low | Low |
| Moses 2005 | High | High | High | High | Low | Unclear | Low |
| Naenni 2017 | Low | Low | Low | Low | Low | Low | Low |
| Basler 2018 | Low | Low | Low | Low | Low | Low | Low |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nemcovsky 2002 | High | High | Low | Low | Low | Low | Low |
| Park 2008 | Low | Low | Unclear | Low | Low | Unclear | Low |
| Schlegel 1998 | High | High | Low | High | Low | High | High |
| Schneider 2014 | Low | Low | High | High | Low | Low | Low |
| Van Assche 2013 | Low | Low | High | Low | Low | Unclear | Low |
| Wessing 2017 | Low | Low | Low | Low | Low | Low | Low |
| Zitzmann 1997 | Low | Unclear | Unclear | Unclear | Low | Unclear | Low |
| Zitzmann 2001 | Unclear | Unclear | Unclear | Unclear | Low | Unclear | Low |
| Jung 2013 | Unclear | Unclear | Unclear | Unclear | Low | Unclear | Low |

**Table 2**

| Reference | Publication date | Follow-up (months) | Group | Intervention | Number of patients | Defect height at baseline mm (SD) | Defect height at re-entry mm (SD) | Defect height change mm (SD) |
|---|---|---|---|---|---|---|---|---|
| Mattout | 1995 | 6.8 | test | Non-resorbable ePTFE membrane | 11 | 4.83 (1.73) | 0.8 (1.48) | 4.04 (1.33) |
| | | | control | DFDBA + non-resorbable ePTFE membrane | 9 | 6.8 (2.65) | 0.33 (0.94) | 6.46 (2.96) |
| Zitzmann | 1997 | NR | test | Particulate xenograft + non-resorbable ePTFE membrane | NR | NR | NR | NR |
| | | | control | Particulate xenograft + resorbable collagen membrane | NR | NR | NR | NR |
| Lorenzoni[a] | 1998 | 6 | test | Particulate autologous bone + Polyglycolid, self-reinforced-PGA resorbable membrane | 38 | 3.9 (1.5) | 1.7 (1.3) | 2.2 (1.41) |
| | | | control | Particulate xenograft and/or particulate autologous bone + non-resorbable ePTFE membrane | 46 | 4.5 (2.0) | 0.9 (1.6) | 3.6 (1.83) |
| Lorenzoni[a] | 1998 | 6 | test | Particulate autologous bone + Polyglycolid, self-reinforced-PGA resorbable membrane | 38 | 3.9 (1.5) | 1.7 (1.3) | 2.2 (1.41) |
| | | | control | Particulate xenograft and/or particulate autologous bone + non-resorbable titanium reinforced ePTFE membrane | 45 | 4.6 (1.6) | 0.9 (1.1) | 3.7 (1.42) |
| Schlegel | 1998 | NR | test | Autogenous bone chips + resorbable polydioxanone membrane | NR | NR | NR | NR |
| | | | control | Autogenous bone chips | NR | NR | NR | NR |
| Carpio | 2000 | 6 | test | Particulate xenograft + non-resorbable ePTFE membrane | 25 | 4.18 (0.39) | NR | 2.26 (0.66) |
| | | | control | Particulate xenograft + autologous bone + resorbable collagen membrane | 23 | 4.39 (0.49) | NR | 2.65 (0.61) |
| Nemcovsky | 2002 | 6-8 | test | Late implants: Particulate xenograft + resorbable collagen membrane | 39 | 6.6 (1.9) | 0.6 (0.74) | 6.0 (NR) |
| | | | control | Delayed implants: Particulate xenograft + resorbable collagen membrane | 39 | 5.4 (1.92) | 1.2 (0.88) | 4.2 (NR) |
| Jung | 2003 | 6 | test | Particulate xenograft + resorbable collagen membrane + rhBMP-2 | 10 | 7.0 (2.7) | 0.2 (0.3) | 6.8 (2.7) |
| | | | control | Particulate xenograft + resorbable collagen membrane | 10 | 5.8 (1.8) | 0.4 (0.7) | 5.4 (2.2) |
| Moses[a] | 2005 | 6-8 | test | Particulate xenograft or beta TCP + autologous bone + resorbable | 73 | 5.3 (2.07) | 1 (0.89) | 4.3 (1.8) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | collagen membrane (Ossix®) | | | | |
| | | | control | Particulate xenograft or beta TCP + autologous bone + non-resorbable ePTFE membrane | 34 | 4.9 (1.07) | 1.1 (0.99) | 3.8 (1.03) |
| Moses[a] | 2005 | 6-8 | test | Particulate xenograft or beta TCP + autologous bone + resorbable collagen membrane (Bio-Gide®) | 52 | 5.1 (1.9) | 1.2 (0.86) | 3.9 (1.65) |
| | | | control | Particulate xenograft or beta TCP + autologous bone + non-resorbable ePTFE membrane | 34 | 4.9 (1.07) | 1.1 (0.99) | 3.8 (1.03) |
| Park[a] | 2008 | 6 | test | Cancellous allograft + resorbable collagen membrane | 9 | 6.23 (3.51) | 1.42 (1.35) | 4.81 (2.4) |
| | | | control | Cancellous allograft | 8 | 5.81 (1.86) | 2.21 (1.96) | 3.6 (1.9) |
| Park[a] | 2008 | 6 | test | Cancellous allograft + acellular dermal matrix | 9 | 6.58 (2.79) | 1.47 (1.19) | 5.11 (1.99) |
| | | | control | Cancellous allograft | 8 | 5.81 (1.86) | 2.21 (1.96) | 3.6 (1.9) |
| Becker | 2009 | 3-5 | test | Particulate xenograft + resorbable cross-linked collagen membrane | 23 | 4.26 (2.18) | 1.26 (1.42) | 3 (2.5) |
| | | | control | Particulate xenograft + resorbable collagen membrane | 26 | 3.44 (1.49) | 1.5 (1.88) | 1.98 (2.13) |
| Jung | 2009 | 6 | test | Particulate xenograft + polyethylenglycol (PEG) resorbable membrane | 19 | 5.95 (1.9) | 0.32 (0.6) | 5.63 (1.84) |
| | | | control | Particulate xenograft + resorbable collagen membrane | 18 | 4.5 (1.54) | 0.25 (0.5) | 4.25 (1.16) |
| Van Assche | 2013 | 12 | test | Particulate autologous bone + HA-60% TCP-40% + resorbable collagen membrane | 14 | 4.4 (2.2) | 0.4 (0.8) | 4.0 (1.84) |
| | | | control | Particulate autologous bone + xenograft + resorbable collagen membrane | 13 | 4.3 (1.5) | 0.2 (0.8) | 4.1 (1.3) |
| Fu | 2014 | 6 | test | Allograft + resorbable bovine pericardium membrane | 13 | 7.62 (1.2) | 0.92 (0.34) | 6.7 (1.07) |
| | | | control | Allograft | 13 | 7.77 (1.03) | 1.92 (0.59) | 5.85 (0.9) |
| Schneider | 2014 | 6 | test | Particulate xenograft + resorbable polylactide/polyglycolide membrane | 19 | 6.3 (2.1) | 1.2 (2.4) | 5.1 (2.26) |
| | | | control | Particulate xenograft + titanium reinforced ePTFE membrane | 21 | 7.2 (2.7) | 0.3 (1.1) | 6.9 (2.35) |
| Lee | 2015 | 4 | test | Particulate xenograft + resorbable cross-linked collagen membrane | 14 | 4.5 (2.2) | 1.1 (1.2) | 2.9 (2.3) |
| | | | control | Particulate xenograft + resorbable collagen membrane | 14 | 5.1 (2.4) | 0.2 (0.6) | 5.0 (2.5) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lee | 2015 | 6 | test | Particulate autogenous or allogenic particles covered by xenograft and resorbable cross-linked collagen membrane | 14 | 3 (1.9) | 0.2 (0.5) | 2.8 (1.71) |
| | | | control | Particulate autogenous or allogenic particles covered by xenograft and resorbable collagen membrane | 13 | 2.8 (1.7) | 0.4 (0.3) | 2.4 (1.57) |
| Merli | 2015 | 6 | test | Beta TCP + resorbable porcine pericardium collagen membrane | 29 | 5.3 (1.9) | 0.5 (0.9) | 4.7 (2.4) |
| | | | control | Particulate xenograft + resorbable collagen membrane | 32 | 4.9 (1.8) | 0.4 (0.8) | 4.5 (2.0) |
| Jung | 2017 | 6 | test | Implant dehiscences left for spontaneous healing | 15 | 3.25 (1.18) | NR | -0.17 (1.79) |
| | | | control | Particulate xenograft + resorbable collagen membrane | 13 | 3.64 (1.37) | NR | 1.79 (2.24) |
| Naenni | 2017 | 6 | test | Particulate xenograft + non-resorbable titanium reinforced ePTFE membrane | 14 | 2.4 (2.1) | 0.2 (0.8) | 2.2 (1.8) |
| | | | control | Particulate xenograft + resorbable collagen membrane | 13 | 4.0 (2.1) | 0.8 (0.9) | 3.2 (1.83) |
| Wessing | 2017 | 6 | test | Particulate xenograft + resorbable collagen membrane (creos xenoprotect®) | 23 | 5.1 (2.1) | 1.0 (1.3) | 4.1 (2.2) |
| | | | control | Particulate xenograft + resorbable collagen membrane (Bio-Gide®) | 24 | 4.9 (1.9) | 1.7 (2.1) | 3.3 (2.8) |

**Table 3**

| Type of membrane | | | | Exposures (n) | Sites (n) | Exposures in % |
|---|---|---|---|---|---|---|
| resorbable | natural | allogenic | acellular dermal matrix | 2 | 9 | 22.22 |
| | | xenogenic | native collagen membrane | 84 | 499 | 16.83 |
| | | | cross-linked collagen membrane | 12 | 53 | 22.64 |
| | synthetic | polyethylene glycol membrane | | 6 | 19 | 31.58 |
| | | polydioxanone /polylactide/polyglycolide membrane | | 28 | 71 | 39.43 |
| non-resorbable | non-reinforced | ePTFE membrane | | 46 | 157 | 29.30 |
| | reinforced | ePTFE membrane | | 24 | 82 | 29.26 |

**Table 4**